b.) Remarks

Claim 16 and 42 have been amended solely for better grammatical structure. Accordingly, no new matter has been added.

Claims 16, 19, 20, 35 and 42-44 are rejected under 35 U.S.C. §103(a) as being obvious over EP 0 850,646, optionally in view of Woodle '633. Additionally, claims 16, 19, 20, 35 and 42-44 are rejected as being obvious over Woodle '633, Woodle '556 and Allen, all in view of EP 0 850 646. The Examiner's bases of rejection are set forth at pages 2-5 of the Office Action. Both rejections are respectfully traversed, and are discussed below in turn.

Initially, however, Applicants would like to briefly discuss the salient features of the present invention and, *inter alia*, its patentable nature over the prior art.

As the Examiner is aware, the present invention relates to pharmaceutical compositions of indolocarbazole derivative(s) encapsulated in liposomes having an average particle size of 120 to 500 nm. The liposomes consist of lipids that are hydrogenated soybean phosphatidylcholine optionally mixed with polyethylene glycol-modified phospholipid.

It is understood that it is desirable, for pharmaceutical liposomes, e.g., liposomes containing active agents, that the active agent not leak from the liposomes when in blood, so drug delivery can be closely controlled. It is also understood that indolocarbazole derivatives are, for whatever reason, among the most leaky of active agents that can be encapsulated in liposomes. One salient feature of the present invention, therefore, resides in Applicants' discovery that such leakage, e.g., (i) specifically of

indolocarbazole derivatives, can be effectively reduced by encapsulating such materials in liposomes, (ii) consisting of hydrogenated soybean phosphatidylcholine (optionally mixed with polyethylene glycol-modified phospholipids) and (iii) having an average particle size of 120-500 nm. This particular combination of features is not suggested by the prior art.

As to the first rejection, EP '646 relied upon as teaching indolocarbazole-containing liposomes of hydrogenated phospholipids and PEG-PSPE. Although the sizes of the liposomes are not taught, Woodle is cited to show that preparing liposomes of different sizes is routine. The Examiner concludes it would be routine to "prepare liposomes of desired sizes with the expectation of obtaining the best possible results." Accordingly, the Examiner states the pending claims are obvious, absent a showing of criticality.

Respectfully submitted, this rejection is without bases in fact or in law. At the outset, it is plain that

> "the examiner has not presented any line of reasoning as to why the artisan would have been motivated to so modify the [EP '646] structure, and we know of none. The Examiner's assertion . . . that the proposed modification would have been an obvious matter of engineering design choice well within the level of skill of one of ordinary skill in the art is a conclusion, rather than a reason."

*Ex parte Garrett*, Appeal No. 580-81 at page 4 (BPAI 1986).

Second, the Examiner has made no showing of record that average particle size is result-effective in liposomes.[1] Third, it is well settled that it is only *prima facie* obvious to vary parameters known to be result-effective. That is to say, where the prior art has not recognized the "result-effective" capability of a particular invention parameter, no expectation can exist that varying the parameter would successfully yield any improvement. *In re Antonie*, 559 F.2d 618 (CCPA 1977).

> In *In re Aller* (citations omitted), the court set out the rule that the discovery of an optimum value of a variable in a known process is normally obvious. We have found exceptions to this rule in cases where the results of optimizing a variable, which was known to be result effective, were unexpectedly good (citations omitted). This case, in which the parameter optimized was not recognized to be a result-effective variable, is another exception (emphasis added). Id at 620.

Accordingly, the Examiner has not made out a *prima facie* case of obviousness.

Further, there is simply no burden for Applicants to "shown criticality". The law is well-settled too that Applicants need not bother to "show criticality" until *prima facie* obviousness is established. *In re Chupp*, 816 F.2d 643 (Fed. Cir. 1987). Yet, without a reference showing the result-effectiveness on varying liposome average particle size, there is simply no *prima facie* obviousness.

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[1] It is understood that liposomes having a particle size of more than 500 nm are rapidly cleared from bloodstream and distributed to tissues *in vivo* (e.g., col. 3, 6-13 in Woodle 633, Fig. 5 in Chem. Pharm. Bull. 41, 599-604 (1993)), but this is simply not relevant to Applicants' parameter of average particle size.

Nonetheless, assuming *arguendo* that *prima facie* obviousness has been made, and solely in order to reduce the issues, the undersigned previously pointed out the evidence of record shows liposomes according to the pending claims (e.g., of hydrogenated soybean phosphatidylcholine (HSPC) containing indolocarbazole derivative (UCN-01) and having average particle sizes of 186 and 130 nm) are significantly (80% improved) more stable in rat plasma over three hours than those of the closest prior art (HSPC liposomes containing UCN-01 and having an average particle size of 109 nm).

In response, the Examiner now states Applicants' arguments are not pursuasive because, variously, (i) they are based on a single experiment, (ii) no statistical evaluation is made, and (iii) the results are not relevant for mixed lipids of HSPC with PEG-modified lipid (see page 3 of the May 24, 2005 Office Action at lines 16-20).[2]

Accordingly, again in order to expedite prosecution, enclosed is a Declaration under Rule 132 of Masahiro Yamauchi, the second-named inventor of the present invention. The Examiner's comments are all addressed by the enclosed Declaration presenting additional Examples 5-8 and Comparative Example 6. That is, as requested by the Examiner, the Declaration presents additional data for liposomes of mixed lipids of HSPC with PEG-modified phospholipid. Additionally, the Declaration presents data for the disparate lipids egg phosphotidylcholine, dipalmitoyl phosphatidylcholine and

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[2] Additionally, the Examiner states (see from page 3, line 20 to page 4, line 2) "[i]t is logical therefore, to assure that the liposomes of EP ['646] have sizes at least less than 400 [nm]." Respectfully submitted, the Examiner continues to misconstrue the claims which recite an average particle size, not a maximum particle size. As well-understood by the skilled artisan, the recited average particle size of 120-500 nm is by no means inherent to EP '646. Moreover, in any event, Examples 1 and 22 of EP '646 show that the preparation is passed 5 times through 0.4 micron filters (400 nm) followed by passage 10 times through 0.1 micron filters (100nm). Therefore, it is clear that these liposomes have both a maximum and an average particle size of well less than 100 nm.

mixed lipids of HSPC, PEG-modified distearoyl phosphoethanolamine and cholesterol, all at various sizes.

As both seen and discussed below, only the liposomes consisting of hydrogenated soybean phosphatidylcholine optionally mixed with polyethylene glycol-modified phospholipid and having an average particle size of 120-500 nm provide reduced indolocarbazole leakage. The data is summarized in Figure 1 at page 7 of the Declaration showing the relationship between leakage (defined as "the remaining ratio") of indolocarbazole derivative UCN-01 and the average particle size of the noted liposomes in rat plasma containing human AGP.

First, as shown in Figure 1 of the Declaration, the liposomes having average particle size of 150 nm (Example 5) and 216 nm (Example 7) achieved an average remaining ratio (85%) that is 240% better than the remaining ratio (25%) obtained by the same materials at 98 nm (Comparative Example 6). Additionally, liposomes made from the mixed lipids of HSPC and PEG-modified phospholipid having average particle size of 152 nm (Example 6) and 213 nm (Example 8) achieved a statistically similar average remaining ratio of 78%.

In contrast, however, liposomes made from other lipids were not nearly as efficacious as the present invention. That is, lipids containing UCN-01 of egg phosphatidylcholine showed a remaining ratio of zero %, lipids of dipalmitoyl phosphatidylcholine showed a remaining ratio of five %, and mixed lipids of HSPC, PEG-modified distearoyl phosphoethanolamine and cholesterol showed a remaining ratio of zero %, irrespective of average particle size.

Thus, in contrast to the assertions in the rejection of record, other lipids do not show similar inhibition of leakage from the liposomes. The advantage achieved by the present invention is obviously of great utility to the skilled artisan and is plainly unobvious in view of the prior art. Accordingly, while Applicants earnestly submit *prima facie* obviousness is not established by EP '646 and Woodle '633, Applicants respectfully submit any such *prima facie* case is necessarily overcome by the attached Declaration.

**If for any reason, the Examiner disagrees that the pending claims are now unobvious over EP '646 in view of Woodle '633, the Examiner is respectfully requested to telephone the undersigned in order to schedule a personal Examiner Interview.**

This leaves, therefore, only the rejection over Woodle '633, Woodle '556 and Allen, in view of EP '646.

As to Woodle '633, Woodle '556 and Allen, the Examiner contends they show all features of the present invention except for an encapsulated indolocarbazole derivative. That is, Woodle '633, Woodle '556 and Allen are said to show liposomes of hydrogenated soy phosphatidyl choline, PEG-DSPE or DSPC having diameters from 160-170 nm. EP '646 is relied upon as showing that indolocarbazole can be encapsulated as well.

However, these primary references are all less relevant than EP '646 since Woodle and Allen all encapsulate insulin and GADF, which do not readily leak from liposomes, in contrast to the indolocarbazole derivative of the pending claims and as

utilized in EP '646[3]. Thus, insulin (or GADF) and indolocargazoles differ in kind and this rejection is overcome for the reasons discussed above; the comparative showing need not compare the claimed invention with all of the cited art (see *In re Fenn*, 208 USPQ 470 (CCPA 1981)), but only with the closest prior art (*In re Holladay*, 584 F.2d 384 (CCPA 1978), *In re Merchant*, 572 F.2d 865 (CCPA 1978); *In re Woods*, 599 (F.2d 1032 (CCPA 1979)). Here, the closest prior art is therefore EP '646 and so this rejection too is met by the accompanying Declaration, which illustrates the patentability of the pending claims over the embodiments of that reference.

**If for any reason, the Examiner disagrees that the pending claims are now unobvious over Woodle '663, Woodle '556, and Allen taken with EPO '646, the Examiner is respectfully requested to telephone the undersigned in order to schedule a personal Examiner Interview.**

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 16, 19, 20, 35 and 42-44 remain presented for continued prosecution.

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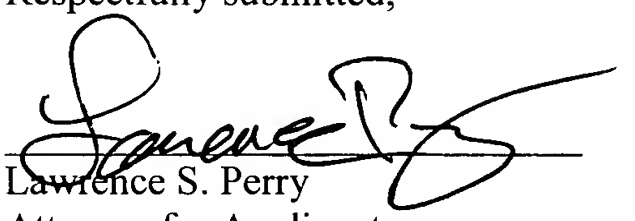
[3] In any event, Woodle '633, '556 and Allen are concerned with the retention of liposomes in blood and teach liposomes with inhibited distribution to tissue. The references do not teach and are unconcerned with liposomes that inhibit leakage of encapsulated actives.

Applicant's undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,



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